

**BILAG Biologics Prospective Cohort:
The Use of Novel Biological Therapies in the Treatment of
Systemic Lupus Erythematosus (SLE).**

(Lay title: Long-term Safety of New Treatments in the Management of SLE)

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1. Background

There have been very few major advances in the treatment of SLE over the past 35 years. In the past 5 years however, there has been an explosion of interest in developing new molecules for the treatment of SLE. A number of approaches have been proposed and are currently in various stages of development including B-cell depleting therapies, IL6 and IL10 blockade as well as inhibition of co-stimulatory molecules, TNF-blockade and lymphodepletion. As these drugs become available for diseases such as RA, off-licence use in SLE is already underway and it is likely that several of these products will gain licences for use in SLE over the next 5 years. However, clinical trials are limited by patient numbers and study duration and therefore are under powered to study potentially important adverse events. In addition, clinical trials tend to exclude patients who have been exposed to other biological therapies in the past and therefore the potential medium-term interactions between various therapeutic approaches cannot be adequately studied.

There have been a number of biologic therapies that have been used in the treatment of SLE on an exceptional, occasional basis; case reports for these therapies include abatacept, infliximab (Hayat et al. 2007; Hayat & Uppal 2007) and etanercept (Micheloud et al. 2006; Takahashi, Naniwa, & Banno 2008). There are currently a number of trials underway examining the safety and efficacy of these therapies, in addition to a number of other biologic therapies.

In addition to these occasionally used biologics, rituximab has been more frequently used successfully in the treatment of SLE patients. Rituximab, an anti-CD20 molecule in open label studies shows good efficacy for the treatment of SLE (Cambridge et al. 2008; Jonsdottir et al. 2008; Leandro et al. 2005; Ng et al. 2007). However, repeat treatment is often required, **after a varying interval**, and there is evidence that when B cells recover and reconstitute, they may have a more naïve phenotype (Anolik et al. 2007). The long-term consequences of these changes, as well as what happens when additional novel therapies are used thereafter, are areas which require study. In addition, rituximab is associated with the development of a Human Anti-Chimeric Antibodies (HACA) response which can blunt the efficacy of subsequent therapies. Again, whether these antibodies have any cross reactivity with other more humanised molecules (e.g. ocrelizumab) remains to be determined and in particular, their influence on efficacy and adverse events to further therapies requires to be known.

Belimumab is a fully human monoclonal antibody that binds to and inhibits the action of soluble human B lymphocyte stimulator (BLyS). Two Phase III trials using belimumab have also recently been reported. In BLISS-52, 865 SLE patients were randomised to either placebo, belimumab 1mg per kg or belimumab 10mg per kg **given monthly**. The response at 52 weeks, was achieved by 46.3% of placebo treated patients compared to 51.4% with belimumab 1mg per kg and 57.6% with belimumab 10mg per kg ($p=0.013$ and 0.0006 respectively) (Trial watch 2009). A second Phase III trial (BLISS-76) randomised 819 patients with active SLE to placebo, 1mg/kg or 10mg/kg of belimumab. At 52 weeks the % of patients achieving the SRI was 33.8% with placebo, 40.6% with 1mg/kg ($p=0.10$ vs placebo) and 43.2% with 10mg/kg ($p=0.021$ vs placebo). (Human Genome Sciences 2009; Trial watch 2009)

Epratuzumab is an anti-CD22 molecule which reduces B-cell numbers by approximately 35-44%. A recent Phase IIB clinical trial compared epratuzumab to placebo in patients with SLE over a 12-week period. The primary end point in this trial was a composite end point with improvement in BILAG scores and no worsening SLEDAI or the Physicians Global Assessment. Using this novel end-point, the treatment advantage of epratuzumab over placebo reached 24.9% at week 12. (Trial watch 2009; UCB Pharmaceuticals 2009)

Abatacept a CTLA4-Ig, licensed for use in RA, reduces co-stimulation also reported a negative trial against a primary outcome of reduced lupus flares. A secondary analysis within the trial did however suggest that patients with arthritis may significantly improve using this agent. (Merrill et al. 2008; Trial watch 2009)

More recently, there has been an increase in other targeted therapies coming into use for the treatment of SLE including some particularly focused on the management of kidney involvement (lupus nephritis -LN) which occurs in approx. 38% of patients with SLE and is associated with significant morbidity and mortality (Hanly 2016). For example, LN and in the BILAG-BR we have found that approx. 42% of patients receiving a biologic had a history of LN as part of their SLE (Bruce unpublished data). Newer therapies are also now being used both after biologics therapies and as first line therapy. These therapies act on cellular pathways and impact on inflammation and on the immune response, so it is important that the long-term safety of these is also monitored in the BILAG BR.

Voclosporin is a novel calcineurin inhibitor (CNI) which is now licensed and has NICE approval for the treatment of active lupus nephritis in combination with mycophenolate mofetil:

“Voclosporin with mycophenolate mofetil is recommended, within its marketing authorisation, as an option for treating active class 3 to 5 (including mixed class 3 and 5, and 4 and 5) lupus nephritis in adults. It is only recommended if the company provides voclosporin with mycophenolate mofetil according to the commercial arrangement” (NICE draft guidance Mar 2023)

Voclosporin, in combination with MMF, achieved its primary endpoint in a phase II trial (AURA-LV) (Rovin 2019) and in the phase III AURORA I trial (Rovin 2021). In AURA-LV the primary endpoint was CRR at 24 week and was achieved by 32.6% voclosporin and 19.3% placebo-treated patients (Rovin 2019). In AURORA 1, CRR at 12 months was achieved by 41% voclosporin vs 23% placebo treated patients (Rovin 2021). A 24-month extension trial (AURORA II) showed stable eGFR and maintenance of low urine protein over the extension period with no new safety signals (Saxena 2022).

A successful model for carrying out such research has been pioneered by the British Society for Rheumatology (BSR) in establishing the BSR Biologics Prospective Cohort (BSRBR) in rheumatoid arthritis. This is a long-term observational study designed and powered to study the development of uncommon long-term adverse events to anti-TNF therapy (principally the development of lymphoproliferative disorders) in RA patients. Although the BSRBR is powered to detect an increase in risk of lymphoma, this wealth of data has been able to address a number of additional questions relating to the safety of these relatively new drugs, including rates of serious infections and the effects of switching between agents (Dixon et al. 2006; Hyrich et al. 2008). The BSRBR is now being extended to capture data on RA patients receiving rituximab.

The model has also been adopted by the British Association of Dermatologists (BAD) who have recently also established a similar prospective cohort study (the British Association of Dermatologists' Biologics Intervention Register, BADBIR) for patients with severe psoriasis, with the main difference being that all data is being collected electronically using secure web-based systems. These studies are likely to become the norm in the UK for following patients treated with biological agents and are now considered the gold standard for collecting real life long-term safety data. The prospective cohort design allows the long-term safety and efficacy of the therapy to

be monitored in real life situations, something that cannot be determined from short-term clinical trials in selected groups of patients.

SLE is a less common disease than either RA or psoriasis. In addition, any study to be established at this time would be an open-label cohort study of patients being treated for an off-licence indication. The limiting factor in doing medium to long term studies of, for example, rituximab in a single centre is numbers and a UK-wide registry would significantly increase the statistical power to study efficacy, safety and biomarker changes in patients receiving these treatments in a 'real world' clinical setting. Also, the small numbers of other drugs precludes any specific conclusions to be drawn from "anecdotal" reporting.

The British Isles Lupus Assessment Group (BILAG) represents a consortium of 10 rheumatology centres across Great Britain who share a specific commitment to the study of SLE. Collaborative work involving this group has led to the development and validation of the original BILAG disease activity instrument (Hay et al. 1993) and current collaborative studies are underway to validate the BILAG 2004 instrument (Isenberg et al. 2005). Other collaborative work has included the CYAZ trial, the LASER study of cardiovascular disease in SLE and the development of the LupusQoL (McElhone et al. 2007), as well as work collaborating with the BSR – Lupus Special Interest Group (BSR-LSIG), the UK Juvenile SLE Group and the Renal Association.

2. Rationale for the Establishment of a Biologics Prospective Cohort for SLE

We propose to establish a BILAG Biologics Prospective Cohort. Considerable expertise in establishing and maintaining such prospective registries is already available in the University of Manchester Arthritis Research UK Epidemiology Unit where both the BSRBR and the BADBIR are being hosted. In the first phase of the BILAG Biologics Prospective Cohort we aim to study clinical response, adverse events and post-treatment biomarker changes in patients receiving biologic agents for the routine management of their SLE. The initial registry would collect data on the safety of the therapy, with hospitalisation for infection as a primary endpoint, in addition to efficacy data (using the BILAG 2004 instrument) to study global and organ specific efficacy of biologic therapies in SLE. Data will also be collected on adverse events post-treatment, particularly according to whether the treating physician continues to co-prescribe concomitant immunosuppressive therapy. In the post-

treatment phase the development of HACA antibodies would be determined as would characteristics of the B-cell population as it is reconstituted. In addition, predictors of response-non-response will be studied.

As previously mentioned, there are a number of other biologic agents that are used for the treatment of SLE, including abatacept, infliximab and etanercept, with further drugs such as alemtuzumab, ocrelizumab, belimumab and tocilizumab being used in the near future. The cohort will be set up to include the registration and follow up of patients treated with these additional biologic agents.

Some biologics are available either as the originator molecule or as biosimilars (e.g. rituximab is available as Mabthera (originator molecule) or as a biosimilar, e.g. Truxima. Biosimilars have the same molecular action. Patients being treated with biosimilars will be recruited to this study.

A number of new biologic, biosimilar and other targeted therapies have since been developed and are being used for the treatment of SLE, with some receiving National Institute for Health and Clinical Excellence (NICE) approval. Some of these drugs are being used after B-cell depletion therapy which raises more important questions regarding long term safety. These agents are all targeted therapies and act on cells, cytokines or other pathways, which play a key role in inflammation and the functioning of the immune system. With each new agent there are concerns as to what the safety profile may be in routine clinical use. Clinical trials of new agents exclude many groups of patients at higher risk of infection, for example those with co-morbidities such as uncontrolled diabetes and also those with other co-morbidities such as renal impairment or coronary heart disease. In routine practice the occurrence of serious adverse events may be higher than in clinical trials.

3. Methods

The BILAG Biologics Prospective Cohort will be established as an independent investigator-led prospective cohort study with the BILAG group acting as the Steering committee.

3.1. Aims

3.1.1. Infection:

The primary aim of establishing the BILAG Biologics Prospective Cohort is to ascertain whether using biologics, biosimilars and other targeted therapies in the ***routine*** treatment of SLE is associated with an increased risk of being hospitalised for infection, compared to SLE patients with similar disease activity receiving conventional therapies.

3.1.2. Efficacy

The secondary purpose of the BILAG Biologics Prospective Cohort is to determine the long-term efficacy of biological therapies, biosimilars and other targeted therapies in the treatment of SLE. This includes achieving a greater understanding of whether certain groups of patients respond differently to specific mode of action agents or groups of agents.

3.1.3. Sequencing

A number of subsidiary questions will also be addressed if sufficient data is collected from additional biologic agents, biosimilars and other targeted therapies, which include the evaluation of differences between these agents, multiple agents concurrently or in sequence in terms of serious adverse effects.

The BILAG Biologics Prospective Cohort will also correct for the influence of potential confounding variables on these outcomes, with data collected on SLE severity, alcohol and smoking and concomitant medications and comorbidities.

3.2. Design

This is a prospective cohort study consisting of two cohorts of patients all of whom will be treated by their consultant according to clinical need and according to the consultant's decision in their usual clinical setting. Patients treated with biological therapies, biosimilars and other targeted therapies (any and not exclusively those mentioned above) will be recruited along with a control group with similar disease characteristics but exposed only to non-biological systemic therapies. Further patients initiating treatment on additional biologic agents, biosimilars and other targeted therapies will also be included. These patients need following up, and even in small numbers, a UK-wide effort through the BILAG Biologics Prospective Cohort presents the ideal opportunity in which to do this. The protocol will be submitted for

MREC approval. Analysis will take into account switching from the control group to a biologic agent, and switching between agents.

The cohort will be modelled on the existing BSRBR and the BADBIR and co-located at Manchester University. Clinicians from the 10 rheumatology centres that make up BILAG will recruit all patients that they treat, commencing treatment with a biologic intervention, that satisfy the inclusion criteria and who consent to take part. Additional collaborating clinicians from the BSR Special Interest Group, the Renal Association and the UK Juvenile SLE Group nationally, will also become recruiting sites and will recruit patients in the same manner.

The cohort aims to recruit all patients from the BILAG centres, and other collaborating sites, receiving **any** biologic, biosimilar or other targeted therapy. Numbers required need to be achievable and sufficient to enable worthwhile comparisons to be made. For example, 220 prospectively recruited patients will be required for each biologic, biosimilar or other targeted therapy included in the biological intervention cohort to allow us to make comparisons in safety data between these and our control population for some of the more common SAEs we are examining. Larger numbers will allow more detailed comparisons of less common AEs, and recruiting even small numbers of the novel targeted therapies will provide important safety information in “rea-world” conditions.

Following registration, for the duration of the study, the BILAG Biologics Prospective Cohort will approach participating consultants, or their delegated contact, to update the records of all patients whether or not they continue on therapy. This will be captured primarily as web-based data entry. Consultants, or their nominated, trained deputy, will be able to view data on their patients and add to this without unnecessary repetition. Paper forms will be available as a substitute for those unable to use a web-based system.

The co-ordinating centre will mail patients with paper forms to gain additional information on their quality of life, lifestyle habits, medication and any health care problems according to the protocol. Where responses from patients or physicians are delayed there will be repeated reminders and phone calls if necessary to ensure the most complete data possible is obtained. This will take the form of a reminder postcard at 2 weeks and a follow-up phone call at 4 weeks if no response is obtained.

When formal follow-up of the last patients entered in the study is complete, BILAG Biologics Prospective Cohort will continue to link the study to NHS England (formerly NHS Digital, HSCIS, the Office for National Statistics) who will process the data and will provide cancer and death information. Patient data will need to be acquired and stored with patient specific information. This will be pseudonymised (e.g. patient number) to protect confidentiality.

3.2.1. Exposed cohort

Inclusion Criteria

1. Patients commencing treatment with a biological, biosimilar or other targeted agent for their SLE at the clinical decision of their treating consultant
2. Patients age 5 years or older
3. a) Willingness and ability to give informed consent for long-term follow-up and access to all medical records (patients 16 years old or older)

or

- b) Willingness and ability of parents to give informed consent for their child and willingness and ability of child to give assent

Exclusion Criteria

1. Unwilling or unable to provide informed consent

Repeat treatments

In routine care, biologics therapies will usually be administered in one of two different methods: as a regular injection / infusion throughout the therapeutic course, or as an intermittent / episodic therapy, for example with some rituximab regimes. In some situations, therefore, a patient will be given the treatment in an intermittent way and a re-treatment will be indicated by a flare of their disease. As the primary aim of the study is to examine the safety of the biologic therapies, when compared to conventional treatments, in patients who flare, and therefore require a retreatment with a biologic in this way, their “study clock” will be reset to time 0, and will receive 3, 6 and 12 monthly post-treatment follow-ups as a newly recruited patient would.

Similarly, patients who switch from conventional therapy to the biologics group, or who switch from one biologic therapy to another, due to lack of efficacy or toxicity issues, for example, will also have their “study clock” reset to zero to ensure the

safety of the newly prescribed biologic can be ascertained, with the appropriate statistical adjustment for such time varying data.

3.2.2. Non-exposed cohort

Many patients with similar disease activity will also be started on more traditional interventions e.g. azathioprine, mycophenolate mofetil, cyclophosphamide etc. A control group will be recruited and will consist of SLE patients from the BILAG centres who are being initiated on standard therapy, including azathioprine, Mycophenolate mofetil (MMF) or cyclophosphamide for active SLE. This will allow us to adjust any future analysis for factors associated with severe SLE of an equivalent level of severity to that for which biologics would be employed.

Inclusion Criteria

1. Patients **newly** commencing treatment (i.e. within one month of starting) with a non-biological, immunosuppressive agent, such as azathioprine, MMF or cyclophosphamide for their SLE at the clinical decision of their treating consultant
2. Patients age 5 years or older
3. a) Willingness and ability to give informed consent for long-term follow-up and access to all medical records (patients 16 years old or older)

or

- b) Willingness and ability of parents to give informed consent for their child and willingness and ability of child to give assent

Exclusion Criteria

1. Patients with any prior exposure to biologic or biosimilar or other targeted agents

If for clinical reasons a 'control' is subsequently started on a biological, biosimilar or other targeted therapy then he/she would switch from the control cohort into the biological cohort.

4. Statistics, sample size and power calculations

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow-up time will be censored in both cohorts if there is switching to another class of biologic therapy and censored in the standard therapy group if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow-up, after the start of therapy. Depending on the events, separate analyses are

undertaken (i) restricting consideration to time on drug, which include the period within 90 days of last injection (ii) within 26 weeks and (iii) all person time following start of therapy (see figure below). Standard time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other differences.

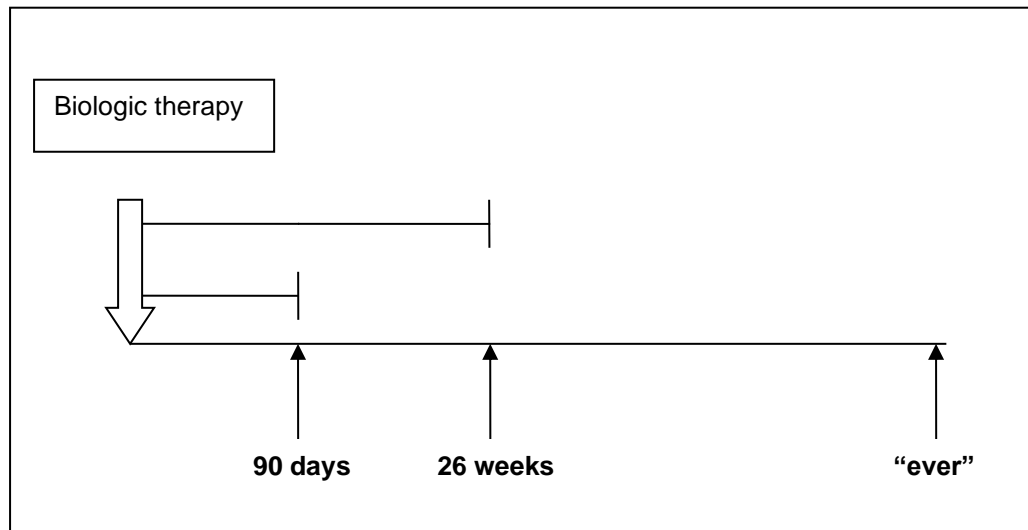


Figure 1:

The primary comparison to consider is whether, compared to other immune therapies, biologics are associated with a doubling of the risk of being hospitalised for infection. This is an important and well recognised serious adverse event (SAE) that can occur in the context of SLE therapy. Secondary analyses will include factors related to both the safety and efficacy of the therapy.

Safety

Secondary outcomes relating to the safety of the therapy will include

- All SAEs on therapy
- Mortality (all cause)

Efficacy

Secondary outcomes relating to the safety of the therapy will include

- Initial clinical response data and predictors of response
- Damage accrual over 3-5 years of follow-up
- Additional outcomes based on biomarker and immune function studies.

A review of the current literature reveals a range of rates that have been suggested for hospitalisation for infection in SLE. In 2 MMF trials (vs. other immunosuppressive regimes), which may be of relevance to the current considerations, rates of hospitalisation for infection in patients taking immunosuppression for lupus nephritis

specifically were 5% over 6 months and 10% over 72 months (Contreas et al. 2004;Ginzler et al. 2005). In addition Houssiau et al in the ELNT trial (cyclophosphamide and azathioprine exposure) 17% of patients were admitted over a 41-month period with infection (Houssiau et al. 2002).

In cohort studies of SLE, a 1992 study (Petri & Genovese 1992) suggested 9% per annum were admitted for infection while an estimate from Bosch et al suggests 9% hospitalisations over 2 years (Bosch et al. 2006) and in the Toronto cohort approx. 13% were admitted over a 5 years period (Gladman et al. 2002). Two recent trials of contraception in SLE followed subjects for 12 months. In each trial 4-6 % of patients per annum were admitted for infection. In one trial there was a particularly high incidence of infection in one subgroup which may have skewed the results upward. However the trials were of milder SLE patients.

Therefore, taking a conservative view and considering the ELNT trial as well as the Bosch, Gladman and Contreras studies (Bosch, Guilabert, Pallares, Cerveral, Ramos-Casals, Bove, Ingelmo, & Font 2006;Contreas, Pardo, Leclercq, Lenz, Tozman, O'Nan, & Roth 2004;Gladman, Hussain, Ibanez, & Urowitz 2002) in particular as showing the lower end of the range, our sample size is based on a rate of 10% of patients being admitted for infection over a 3-year period. Using this rate of infection admissions in the control group, 220 patients per group would be needed to demonstrate a doubling of the rate of admissions in the biological agent exposed patients over a 3 year period with 80% power at the 5% level. If the rates are closer to 15% over 3 years then 130 patients per group will achieve sufficient power (see appendix 1).

These are conservative estimates and if numbers of admissions are considered (i.e. multiple admissions per patient) then power is greater, however this data is difficult to estimate from the literature. Similarly, if the absolute rates are higher in SLE overall, then the power will be increased.

We would estimate that once operational approximately 75 patients per year will be recruited to each arm in each of the first 3 years. Once established then we estimate approximately 100 patients per annum thereafter. We would plan initially to follow patients for the first 3 years after first exposure to a new biological agent with extended follow-up the subject of future plans.

Given the anticipated recruitment rates, we aim to recruit the relevant numbers in the first 3-4 years of the registry and within 4-6 years will have adequate follow-up data to perform a primary analysis.

Patients recruited newly exposed to other biologic agents (for example infliximab, etanercept, abatacept or alemtuzumab) will also be recruited following the same sample size and power calculations, although these will be less frequent due to the current policy of occasional, exceptional prescribing of these agents in this patient group. It is however important to follow-up these patients within the BILAGBR as the long term safety and efficacy of other biologic therapy in SLE requires monitoring, regardless of the numbers initially receiving the therapy. The fact that many of these will be used after rituximab means that valuable data will be recorded on whether specific “sequences” of biologic therapy have any obvious adverse events.

Extension to follow-up and recruitment figures

Following preliminary analyses identifying a lower rate of hospitalisation for infection than anticipated in the cohort, we have been successful in obtaining funding to allow us to increase recruitment into the following cohorts:

- New biologic and biosimilar starts
 - Including, but not limited to, new rituximab starts; new belimumab starts (up to a minimum of 220 per group); any other biologic or biosimilar start
- Any new targeted therapy start, including, but not limited to:
 - Voclosporin
 - Baricitinib or other JAK inhibitor
- Control patients;

as well as to continue recruitment rituximab retreatment patients, in line with the NHS England policy.

This extension will also allow us to:

- 1) Follow existing patients and achieve a minimum of three years follow-up data per patient already in the study, but also extend follow-up up to 15+ years of follow-up for those early recruits, to increase the person years of follow-up in the study. This will increase the power of the study to detect a doubling in the risk of hospitalisation for infection, allow us to examine subgroups of infections (including less common opportunistic infections) and also examine

new secondary outcomes including cardiovascular disease and hypogammaglobulinaemia. Hypogammaglobulinaemia is now being observed after long term exposure to immune suppressive medications and may be a risk factor for late onset infections. Longer term observation of a larger cohort will allow us to examine this emerging problem.

- 2) Continue collecting biological samples to examine predictors of good or poor response to therapy. This was stopped December 2022
- 3) Analyse data arising from flagging patients with NHS England for cancer and death to ensure we have complete data for these outcomes.

5. Auditing the conduct of the study and research governance

The following coordinated program will ensure quality control

1. Training of staff
2. Online manual will be provided for clinicians to send in quality data, including worksheets for collection of data
3. Quality checks will be made for all data received (i.e. scanning for completeness, errors and database examined for inconsistencies.)
4. Selected serious adverse events (SAEs) will be checked against a set of predefined validation criteria

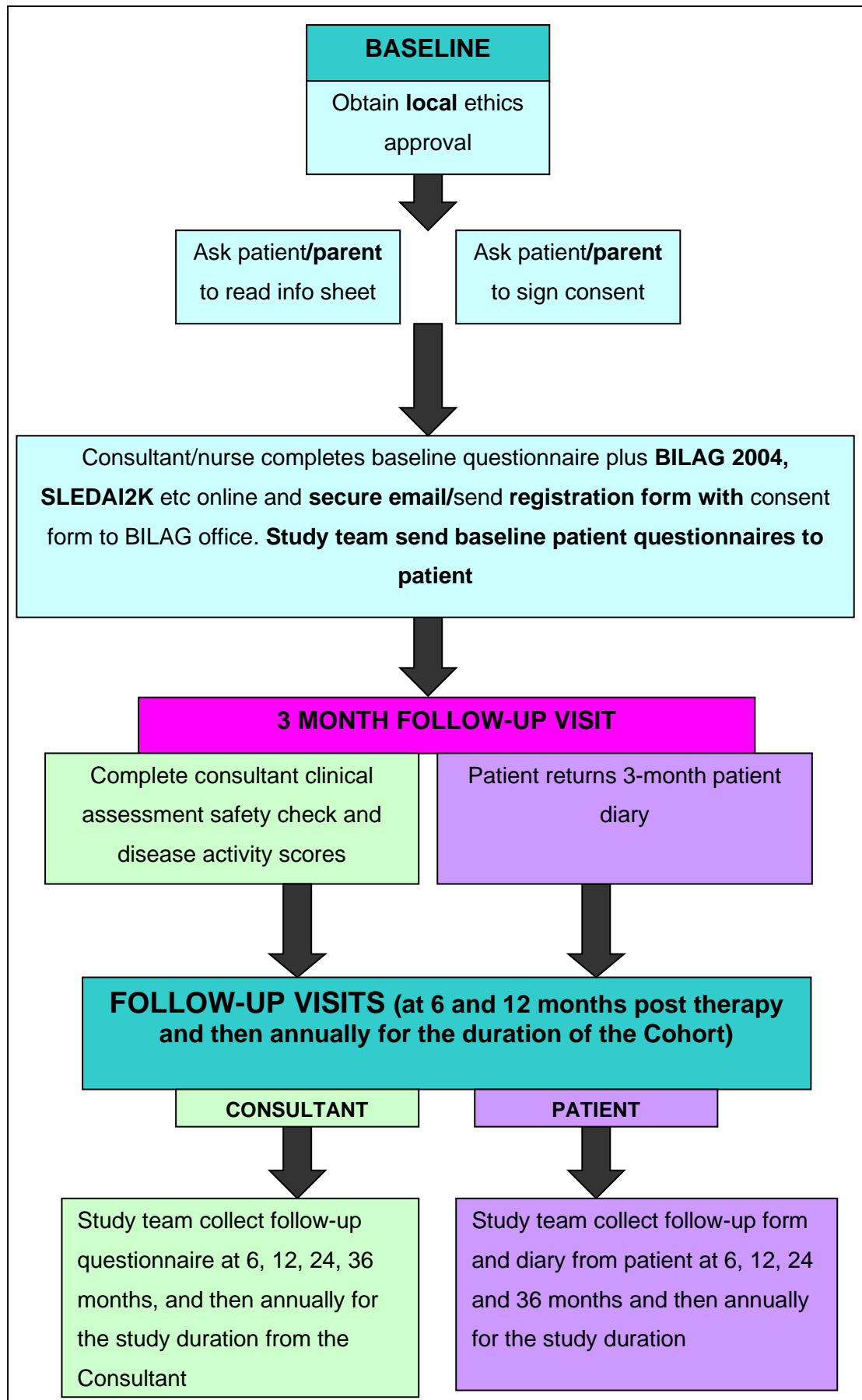
6. Summary Study flow charts

Data captured	Time post therapy					
	Baseline	3 months	6 months	12 months	24 months	36 months and then annually thereafter until study end
Consent	✓					
Patient ID	✓					
Clinical assessment	✓	✓	✓	✓	✓	✓
Co-morbidities	✓					
Concomitant medications	✓	✓	✓	✓	✓	✓
Pregnancy*	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓
SLE details						
BILAG Index 2004	✓	✓	✓	✓	✓	✓
SLEDAI-2K	✓	✓	✓	✓	✓	✓

SLICC Damage Index	✓			✓	✓	✓
Prior therapy	✓					
Patient Questionnaire	Patient questionnaires will only be collected for the first 3 years of follow-up to reduce the impact on patients					
EuroQol / EQ5D	✓	✓	✓	✓	✓	✓
SF-36	✓	✓	✓	✓	✓	✓
LupusQoL	✓	✓	✓	✓	✓	✓
Patient diary	✓	✓	✓	✓	✓	✓
Employment	✓	✓	✓	✓	✓	✓
Drinking	✓	✓	✓	✓	✓	✓
Smoking	✓	✓	✓	✓	✓	✓
Women's health	✓	✓	✓	✓	✓	✓
<u>Bloods (drawn at routine monitoring time points only)</u>	Stopped December 2022					
Basic laboratory values, e.g. Auto antibody profiles Complement fractions Total cholesterol HDL Fasting blood glucose ESR/CRP Immunoglobulins Serology	✓					
<i>Renal biopsy (excess tissue from Pathology stores)</i>	✓**					

***Pregnancy: Specific prompts in the consultant follow-up forms with additional questionnaires if yes to follow specific outcome.**

** Renal biopsy tissue from up to five years before treatment may be collected from Pathology stores at any point following consent.



7. Baseline data

It will be necessary to collect comprehensive baseline data to allow us to adjust for potential confounders in the analysis. To protect the confidentiality of participants, a unique patient identifier will be assigned to each patient on registration. Each participant's identifiable data will then be stored separately from the data to be stored in the cohort study.

Ascertainment of data will be from a combination of methods: patient interview and examination by their doctor or a trained deputy, e.g. research nurse, patient questionnaire and patient diaries. Data will be entered online by the patient's doctor (or allocated trained deputy) using a secure web-based data entry system. The patient's record will be identified by the unique study ID only.

7.1. Patient Identification (to be stored separately for confidentiality)

- Surname
- Forenames
- Address
- Telephone number
- Gender
- Date of Birth
- NHS number (Chi number Scotland) (health and care number Northern Ireland)
- Hospital unit number if above not known
- Lead Consultant(s) for their SLE
- Code for Centre

7.2. Data Collected to appear in cohort study

- Patient identification unique number
- Code for centre
- Gender
- Ethnicity
- Date of Birth
- Date of registration
- Employment status

7.3. Consultant and nurse collected information (see current version of the Consultant data collection Questionnaire)

- Baseline examination – to include blood pressure, height, weight, BMI and waist circumference
- Comprehensive SLE details – to include ACR criteria met and timing of diagnosis
- Biologic, biosimilar or other targeted therapy data (in treatment cohort only) – to include organ system responsible for treatment, previous treatments and reasons for biologics treatment
- Baseline activity of SLE and health status – to include use of BILAG 2004 Index (Isenberg, Rahman, Allen, Farewell, Akil, Bruce, D'Cruz, Griffiths, Khamashta, Maddison, McHugh, Snaith, Teh, Yee, Zoma, & Gordon 2005), SLEDAI 2K (Gladman, Ibanez, & Urowitz 2002), SLICC/ACR Damage Index (Gladman et al. 1996)
- Current and prior therapy – to include exposure to biologic, biosimilar and other targeted therapies as well as non-biologic immunosuppressive drugs, Glucocorticoid exposure from time of SLE diagnosis, Antimalarials, NSAIDS
- Risk factors for infection – to include hepatitis B, hepatitis C, leg ulcers, catheterisation, hyposplenism, splenectomy
- Vaccination history
- Medical history and co-morbidity data - to include angina, heart attack, stroke, epilepsy, asthma, renal disease, raised creatinine, immunodeficiency syndromes (for full list see current version of the questionnaire)
- Concomitant medications
- Results from routine laboratory tests within the previous 6 months, to include:
 - Auto antibody profiles
 - ANA, Ds DNA, Ro, La, Sm, RNP, Scl-70, Centromere
 - Complement fractions
 - C3, C4
 - Total cholesterol
 - HDL
 - Fasting blood glucose
 - ESR/CRP
 - Immunoglobulins

7.4. Patient collected information (see current versions of the Patient data collection Questionnaires)

- Health status and quality of life data to be collected to include instruments such as:
 - EQ5D (2 mins) (The EuroQol Group 1990)
 - SF-36 (10 mins)
 - LupusQoL (10 mins) (McElhone, Abbott, Shelmerdine, Bruce, Ahmad, Gordon, Peers, Isenberg, Ferenkeh-Koroma, Griffiths, Akil, Maddison, & Teh 2007)
 - lifestyle questionnaire (10 mins)
 - Smoking status
 - Alcohol consumption
 - Women's health
 - CHU9D (<16s only)
 - CHAQ/CHQ (<16s only)
 - patient diary recording hospital admissions, visits to outpatients and medications

7.5. Laboratory investigations

As of December 2022 there will have been adequate samples collected for the BILAG BR sample analysis and therefore there will be no further collection needed
Biological samples will be collected from each patient and the BILAG group will coordinate the scientific questions that can be addressed using the relevant material.

A DNA repository will also be established for pharmacogenetic analysis in particular we are interested in predictors of severity and clinical response. Such genes reported to alter phenotype and clinical response in SLE include, complement pathway genes, mannose binding lectin, FCgamma receptor 2A and 3A as well as interferon responsive genes.

DNA will be collected at baseline only, with bloods for serum analysis collected at baseline and at 6 and 12 months post therapy. These blood samples will be taken at the same time as routine bloods are taken. If the patient is not due a routine blood test, then no blood will be collected for that visit and the blood will be collected at the next routine blood test, either at the hospital or elsewhere, e.g. the local health

centre. The patient will be given the opportunity to opt into blood collection separately from the rest of the study.

A urine sample is routinely taken from SLE patients as part of standard of care screening for nephritis and possible infection, the residual sample will also be saved at baseline and at 3, 6 and 12 months post therapy from each patient. This sample will therefore be aliquoted from a routine urine sample. If the patient is unable to provide a routine urine sample, then no urine will be collected from the patient at this visit and the urine will be collected at the next routine appointment.

Samples will also be collected at the baseline of any retreatment course, to monitor immunoglobulin levels at retreatments, but no further follow-up bloods will be collected

A kidney biopsy is frequently taken as part of routine clinical care in lupus nephritis patients. Formalin-fixed paraffin-embedded renal biopsy samples are routinely stored after diagnostic use. The blocks commonly contain surplus renal tissue that is no longer needed for clinical diagnostic purposes. From time to time, we may seek the lead clinician's permission to access this 'excess' tissue in batches. If permission is given, the hospital will ensure that it has patients' permissions to access their 'excess' tissue. Where permission is given, renal samples will be collected prospectively (from any future biopsies) and from biopsies that have been performed before a change of treatment within the previous five years. We will collect blocks from adult patients with consent. Following consent, a member of the BILAG BR study coordination team will liaise with the hospital pathology service to collate samples. We will then arrange their secure dispatch using a tracking courier service with an inventory card providing the relevant BILAG BR patient ID for each block. Blocks will be sent to a researcher specialising in renal transcriptomics at Imperial College London (ICL) Department of Medicine. Both the member of the BILAG BR team and the ICL researcher will have current GCP certification and will have undergone information governance training.

Process of retrospective consent for use of renal tissue in paraffin blocks: All prospective patients will have the opportunity to consent for use of their paraffin blocks as part of the standard consent procedure. For existing patients, the hospital clinical team will identify SLE patients who are BILAG BR participants and who already had a renal biopsy, either at the time of diagnosis or at the time of a

treatment change. Participants will then be contacted by the clinical or study team in their treating centre to say to expect to receive further information about this change to the study in the post. The BILAG BR study coordination team will then write to these patients, and will include a supplementary patient information sheet specifically for provision of excess renal tissue, a supplementary consent form and a stamped addressed envelope for its return to the study coordination team at the University of Manchester.

DNA analysis:

Future analyses will involve the analysis of genes with the potential to predict clinical and drug-specific outcomes of SLE, including genes involved in the susceptibility and pathogenesis of SLE as well as genes in the relevant pharmacogenetic pathways. Such genes include complement pathway genes, mannose binding lectin, FCgamma receptor 2A and 3A as well as interferon responsive genes.

Analysis will be undertaken when sufficient samples have been collected and the relevant outcome is known. This work will be performed by investigators within the BILAG group or by investigators collaborating with BLAG.

Blood, urine and renal tissue analysis:

The blood and urine will be used to analyse serological and biochemical markers that may predict clinical response and specific clinical outcomes in SLE patients, for example urinary MCP-1 and urinary TGF β , and also serum autoantibodies, endothelial microparticles and VEGF.

On arrival of the paraffin blocks at Imperial College London, the researcher will remove renal tissue from the block. The renal tissue taken for research will only be identifiable from this point forward by the BILAG BR patient ID number and date of original sample collection. The excess renal tissue will be used to analyse transcriptomic markers that may predict clinical response and specific clinical outcomes in SLE patients.

The remainder of the paraffin block will be returned securely to the originating hospital. Due to the nature of these samples, there may be very little to no excess tissue available when the block is provided to Imperial College London. As such, the block may be returned with no visible tissue remaining. This can also occur following

clinical assessment of the tissue for histology. The block itself will still be returned to the originating hospital for traceability.

Analysis will be undertaken when sufficient samples have been collected and the relevant outcome is known. This work will be performed by investigators within the BILAG group or by investigators collaborating with BILAG.

Patients will be given the opportunity to consent to their samples being shared with other collaborating groups. This will allow applications for samples to be considered by the steering group.

8. Follow-up data

Recorded at 3, 6, 12, 24 and 36 months post therapy and then annually thereafter for the duration of the project. The following data will be collected:

8.1. Consultant Follow-up

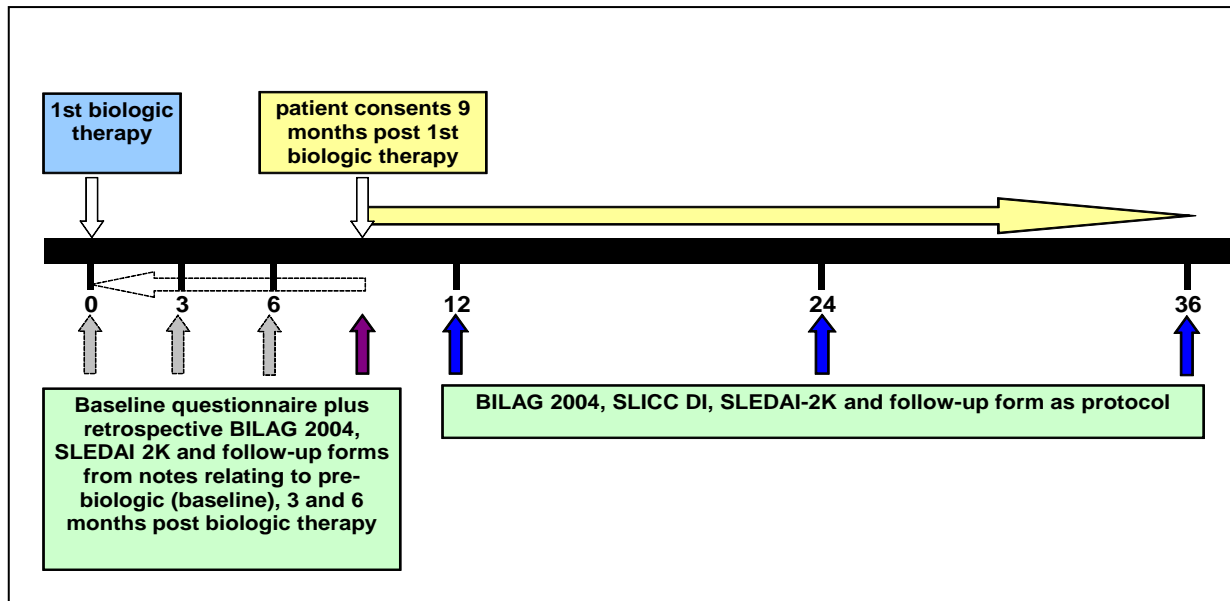
- Changes to the patient's biological therapy and reasons for changes
- Change in the patient's concomitant medication
- Information on any adverse events – with prompts for serious infection, infusion reactions, immunological reactions. Adverse events will be classified according to the new pharmaceutical standard Medical Dictionary for Regulatory Authorities (MedDRA) coding (latest version)
- Current SLE activity and health status
- Vital status
- Pregnancy status
- Results from routine laboratory tests within the previous 6 months, to include (where relevant):
 - Auto antibody profiles
 - ANA, Ds DNA, Ro, La, Sm, RNP, Scl-70, Centromere
 - Complement fractions
 - C3, C4
 - Total cholesterol
 - HDL
 - Fasting blood glucose
 - ESR/CRP
 - Immunoglobulins

8.2. Postal questionnaire to patients and patient diaries (to be collected for the first 3 years of follow-up only)

- Health status and quality of life data to be collected to include the instruments such as:
 - EQ5D (The EuroQol Group 1990) (2 mins)
 - SF-36
 - LupusQoL (10 mins) (McElhone, Abbott, Shelmerdine, Bruce, Ahmad, Gordon, Peers, Isenberg, Ferenkeh-Koroma, Griffiths, Akil, Maddison, & Teh 2007)
 - lifestyle questionnaire (10 mins)
- Add any missing data from registration
- Patient diaries
 - New hospital referrals or admissions
 - New medications

8.3. Retrospectively recruited patients

As described in section 3.2.1., participants are eligible to participate in the study, and be recruited into the biologics arm if they have had their first treatment with a biologic therapy in the last 12 months. Some patients may therefore have been recruited after their 3 and 6 months follow-up visits would have taken place. To ensure that important information is not missed relating to the time period immediately after their biologic therapy, the consultant follow-up questionnaire, BILAG 2004 and SLEDAI 2K will be completed from their notes to correspond to the participant's baseline, 3 and 6 months visit, where necessary. The example below outlines this for a patient recruited 9 months post initial biologic therapy



8.4. NHS England

All exposed and control individuals will be “flagged” with NHS England for continuous surveillance and notification of mortality and the development of any malignancy. A copy of the death certificate will be obtained for those who die and details of type and site of cancer for those who develop a malignancy will be provided.

9. COVID-19 pandemic and the BILAG BR

The aim of the BILAG BR is to examine the safety and effectiveness of biologics therapies in the treatment of Systemic Lupus Erythematosus (SLE), with the primary outcome hospitalisation for infection. During the COVID-19 pandemic, many patients with Systemic Lupus Erythematosus (SLE) have been advised to undertake social shielding by the government, as this patient cohort is at increased risk of infections in general, due to the intrinsic nature of the disease, the use of immunosuppressant medication and prevalence the of co-morbidities such as renal failure.

There is theoretical evidence that glucocorticoids, immunosuppressive agents and biologic agents can significantly impair immune responses to Covid-19 infection. It is also known that such agents, alone or in combination, may impair other vaccine responses e.g. *streptococcus pneumoniae* and influenza. The UK government are now offering COVID-19 vaccination to this cohort of patients, but it remains unknown to what extent this will affect infection rates and as such, how it will influence our

primary outcome. Therefore with the recent emergence of COVID-19 and its profound effect on infection-related outcomes (our primary outcome) and the more recent vaccine roll-out, it is important we understand this better so we can better interpret our registry analyses in the face of the global pandemic. This issue falls under the safety remit of the BILAG-BR and we therefore need to investigate the clinical and immune effects of Covid-19 infection and vaccination in this population in order to more precisely interpret our primary outcome and ultimately to advise and manage patients more effectively.

Supplementary consent will be sought electronically from those patients who are participating in the patient mailing for the BILAG BR. There are three strands to these investigations, and patients can consent to each section individually:

9.1. A Covid-19 patient survey (to establish behaviours) (This section was stopped in 2022)

In the current pandemic, participants are attending clinics less frequently, and the participant mail-out has been temporarily paused. This online survey will allow calculation of the incidence of Covid-19 infection in this patient cohort. Data collected on treatment and individual behaviour will be used help to allow stratification of patient risk.

1. Participants will be provided with a patient information sheet outlining the reason for the online survey and provided with a web link that will direct them to the electronic consent form, which will record the patient responses to the consent questions directly into the main study database.
2. Participants will verify their details by entering their unique study ID, along with their month and year of birth
3. Once the patient has electronically consented to each item on the consent form, they will be asked to confirm their consent
4. They will then be redirected to the online covid-19 survey, linked to their unique study ID
5. If the participant does not wish to complete the survey electronically, or is unable to do so, they have the option to complete a paper copy and return in the post, or to telephone the researcher (Dr Mia Rodziewicz). She will log into the consent form for the participant and take proxy consent. The “proxy consent” box will be ticked to confirm this.
6. The covid-19 survey will then be completed by the researcher, while speaking to the participant.

9.2. A home dried blood spot testing (to check for Covid-19 antibodies)

Those who consent to a self-administered home pin prick blood test will be sent this, by the BILAG BR study team, via the post. Instructions will be provided for the taking of the samples, and they are returned in the post to the study team. The samples will be analysed by researchers at the University of Manchester. This will allow the serological correlation with those patients who report previous Covid-19 infection. It will also enable the examination of any difference in presence and duration antibody response compared to the general population (data already publically available).

9.3. Whole blood samples taken at their usual centres of care (detailed evaluation of B cell populations).

Patients who receive (or plan to receive) a Covid-19 vaccine and who require blood tests as part of their usual care, will be given an option for 15mls extra to be taken for return and analysis at The University of Manchester, both pre- and/or post-vaccination. This will allow detailed study of immune responses to Covid-19 infection and vaccination. Preliminary work from our group has already identified demonstrated differences in immune responses of those patients with severe Covid-19 infection versus those who develop mild disease. Expansion of the work to SLE patients would allow detailed exploration of the mechanisms underlying any differences to infection and immunisation observed in the first two parts of the study.

Participants will be contacted by post, to invite them to participate in the covid-19 related data collection. Any participants who have opted out of receiving mailings from the BILAG BR will not be sent the covid-19 mailing.

Data storage and confidentiality

Survey data

Non-patient identifiable survey data will be entered into a University of Manchester approved survey system (<https://www.qualtrics.manchester.ac.uk/>). No patient identifiable data will be collected through the survey. Qualtrics survey tool stores data in the EU with UKGDPR now in force “These UK transfer rules broadly mirror the EU GDPR rules, but the UK has the independence to keep the framework under review.” Quote from International transfers after the UK exit from the EU Implementation

Period | ICO (<https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/international-transfers-after-uk-exit/>)

Survey data collected will only be downloaded in an excel data format, onto the secure University of Manchester shared drive for analysis.

Consent forms

Patients will provide their consent for this section of the research either electronically or by return of paper copies. Validation of the patient ID for electronic consent will be provided using the patient's unique study ID, and month and year of birth, which will be auto-cross referenced against the study database. No patient identifiable data will be collected electronically.

Paper copy consent forms will be posted to the BILAG BR Offices in pre-addressed, prepaid envelopes. They will be stored in secure in locked filing cabinets, in offices that are alarm and lock protected. The BILAG BR will keep this identifiable information for 10 years after the study has finished and it then will be securely destroyed.

10. Analysis

10.1. Primary endpoint for evaluation

- Any infection requiring hospitalisation

10.2. Secondary endpoints for evaluation

Secondary endpoints fall into two categories; those to do with the safety of biologic therapy in patients with SLE, and those concerning the efficacy of biologic therapy in SLE patients

10.2.1. Safety

- Serious adverse event (**according to WHO definition**), other than death
- Death and cause of death
- Malignancy

10.2.2. Efficacy

- Clinical response
- Damage

10.3. Hypotheses to test

1. Biologic therapy is associated with an increase in hospitalisation for infection when compared to patients on conventional, non-biologic therapy
 - a. Increased risk is related to the duration of therapy
 - b. Baseline characteristics determine increased risk, especially prior therapy
2. Biologic therapy reduces the disease activity when compared to patients on conventional, non-biologic therapy
3. Biologic therapy reduces the damage accrued when compared to patients on conventional, non-biologic therapy
4. Biologic therapy exposure reduces steroid use over 3 years in SLE
5. Certain longitudinal combinations of treatment carry higher risks
6. Novel genetic and serum/urine biomarkers will predict changes in inflammatory disease burden over time in SLE patients treated with biological therapy.

10.4. Analytic approach

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow up time will be censored in the standard therapy cohort if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow up, following the start of therapy. Depending on the events, separate analyses are undertaken (i) restricting consideration to time on drug, which includes the period within 90 days of last injection (ii) including the window 26 weeks after the last injection and (iii) all person time following start of therapy e.g. malignancy. Time-dependent regression analyses will be undertaken to compare event rates between groups after adjusting for baseline and other differences.

To reduce the impact of bias, patients who are recruited into the study following the NHS Commissioning Statement, who are not receiving their first course of Rituximab, will be recorded as a separate sub-group of the biologics cohort, to allow for separate analyses to be carried out on this group.

10.5. Interim Analyses

Interim analyses will be undertaken at appropriate intervals when sufficient person years of exposure have been accumulated in the exposed group. Such analyses will be a guide to the ultimate levels of recruitment and length of follow up required.

Decisions as to the timing of publications and the need for continued follow up and/or recruitment can only be taken in the light of results from such analyses.

A Data Monitoring and Ethics Committee (DMEC) will be established, analogous to a Data Safety & Monitoring Board established for major clinical trials. The DMEC will be independent of the principal investigators and also of any of the pharmaceutical industries involved, and will have the power to request interim analyses and advise on the timing and nature of any publications. The DMEC will include one epidemiologist, a rheumatologist and a statistician.

11.Roles of interested parties

The University of Manchester will be the sponsor of the BILAG Biologics Prospective Cohort and BILAG will have ownership of the data. The project will be steered by a steering group and data monitoring and ethics committee (DMEC) under the auspices of the BILAG and will operate independently from direct industry involvement. The University of Manchester study coordination team may require access to patients' medical notes to check that the study is being carried out correctly, and exceptionally to assist hospital sites in collecting and recording BILAG BR clinical data that is missing from the BILAG BR database.

11.1. Role of pharmaceutical companies

- Funding
- Access
- Intellectual Property

11.2. Role of BILAG

BILAG will be the owner of the data that emerge from the study and will form the Steering Committee. The study coordinator will report on a quarterly basis to such committees that the BILAG deem appropriate. The membership of the DMEC will be subject to the approval of BILAG.

References

Anolik, J. H., Barnard, J., Owen, T., Zheng, B., Kemshetti, S., Looney, R. J., & Sanz, I. 2007, "Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy", *Arthritis Rheum.*, vol. 56, no. 9, pp. 3044-3056.

Bosch, X., Guilabert, A., Pallares, L., Cerveral, R., Ramos-Casals, M., Bove, A., Ingelmo, M., & Font, J. 2006, "Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients", *Lupus*, vol. 15, no. 9, pp. 584-589.

Cambridge, G., Isenberg, D. A., Edwards, J. C., Leandro, M. J., Migone, T. S., Teodorescu, M., & Stohl, W. 2008, "B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response", *Ann.Rheum.Dis.*, vol. 67, no. 7, pp. 1011-1016.

Contreas, G., Pardo, V., Leclercq, B., Lenz, O., Tozman, E., O'Nan, P., & Roth, D. Sequential therapies for proliferative lupus nephritis. *N Engl J Med.* 350[10], 971-980. 2004.

Ref Type: Generic

Dixon, W. G., Watson, K., Lunt, M., Hyrich, K. L., Silman, A. J., & Symmons, D. P. 2006, "Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register", *Arthritis Rheum.*, vol. 54, no. 8, pp. 2368-2376.

Ginzler, E. M., Dooley, M. A., Aranow, C., Kim, M. Y., Buyon, J., Merrill, J. T., Petri, M., Gilkeson, G. S., Wallace, D. J., Weisman, M. H., & Appel, G. B. 2005, "Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis", *N.Engl.J.Med.*, vol. 353, no. 21, pp. 2219-2228.

Gladman, D., Ginzler, E., Goldsmith, C., Fortin, P., Liang, M., Urowitz, M., Bacon, P., Bombardieri, S., Hanly, J., Hay, E., Isenberg, D., Jones, J., Kalunian, K., Maddison, P., Nived, O., Petri, M., Richter, M., Sanchez-Guerrero, J., Snaith, M., Sturfelt, G., Symmons, D., & Zoma, A. 1996, "The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus", *Arthritis Rheum.*, vol. 39, no. 3, pp. 363-369.

Gladman, D. D., Hussain, F., Ibanez, D., & Urowitz, M. B. 2002, "The nature and outcome of infection in systemic lupus erythematosus", *Lupus*, vol. 11, no. 4, pp. 234-239.

Gladman, D. D., Ibanez, D., & Urowitz, M. B. 2002, "Systemic lupus erythematosus disease activity index 2000", *J.Rheumatol.*, vol. 29, no. 2, pp. 288-291.

Hay, E. M., Bacon, P. A., Gordon, C., Isenberg, D. A., Maddison, P., Snaith, M. L., Symmons, D. P., Viner, N., & Zoma, A. 1993, "The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus", *Q.J.Med.*, vol. 86, no. 7, pp. 447-458.

Hayat, S. J. & Uppal, S. S. 2007, "Therapeutic efficacy and safety profile of infliximab in active systemic lupus erythematosus", *Mod.Rheumatol.*, vol. 17, no. 2, pp. 174-177.

Hayat, S. J., Uppal, S. S., Narayanan Nampoory, M. R., Johny, K. V., Gupta, R., & Al-Oun, M. 2007, "Safety and efficacy of infliximab in a patient with active WHO class IV lupus nephritis", *Clin.Rheumatol.*, vol. 26, no. 6, pp. 973-975.

Houssiau, F. A., Vasconcelos, C., D'Cruz, D., Sebastiani, G. D., Garrido Ed, E. R., Danieli, M. G., Abramovicz, D., Blockmans, D., Mathieu, A., Direskeneli, H., Galeazzi, M., Gul, A., Levy, Y., Petera, P., Popovic, R., Petrovic, R., Sinico, R. A., Cattaneo, R., Font, J., Depresseux, G., Cosyns, J. P., & Cervera, R. 2002, "Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide", *Arthritis Rheum.*, vol. 46, no. 8, pp. 2121-2131.

Human Genome Sciences. Human Genome Sciences and Glaxo Smith Kline announce positive results in second of two Phase 3 trials of BENLYSTA™ in systemic lupus erythematosus. www.hgsi.com/latest/human-genome-sciences-and-glaxosmithkline-announce-positive-results-in-second-of-two-phase-3-trials-of-benlysta-in-systemic-lupus-erythema.html , last accessed Nov 28th 2009. 2009.

Ref Type: Generic

Hyrich, K. L., Lunt, M., Dixon, W. G., Watson, K. D., & Symmons, D. P. 2008, "Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug", *Rheumatology.(Oxford)*, vol. 47, no. 7, pp. 1000-1005.

Isenberg, D. A., Rahman, A., Allen, E., Farewell, V., Akil, M., Bruce, I. N., D'Cruz, D., Griffiths, B., Khamashta, M., Maddison, P., McHugh, N., Snaith, M., Teh, L. S., Yee, C. S., Zoma, A., & Gordon, C. 2005, "BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus", *Rheumatology.(Oxford)*, vol. 44, no. 7, pp. 902-906.

Jonsdottir, T., Gunnarsson, I., Risselada, A., Henriksson, E. W., Klareskog, L., & van Vollenhoven, R. F. 2008, "Treatment of refractory SLE with rituximab plus cyclophosphamide: clinical effects, serological changes, and predictors of response", *Ann.Rheum.Dis.*, vol. 67, no. 3, pp. 330-334.

Leandro, M. J., Cambridge, G., Edwards, J. C., Ehrenstein, M. R., & Isenberg, D. A. 2005, "B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients", *Rheumatology.(Oxford)*, vol. 44, no. 12, pp. 1542-1545.

McElhone, K., Abbott, J., Shelmerdine, J., Bruce, I. N., Ahmad, Y., Gordon, C., Peers, K., Isenberg, D., Ferenkeh-Koroma, A., Griffiths, B., Akil, M., Maddison, P., & Teh, L. S. 2007, "Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus", *Arthritis Rheum.*, vol. 57, no. 6, pp. 972-979.

Merrill, J. T., Neuwelt, C. M., Wallace, D. J., Shanahan, J. C., Latinis, K. M., Oates, J. C., Utset, T. O., Gordon, C., Isenberg, D. A., Hsieh, H. J., Zhang, D., & Brunetta, P. G. 2008, "Efficacy and Safety of Rituximab in Patients with Moderately to Severely Active Systemic Lupus Erythematosus (SLE): Results from the Randomized, Double-blind Phase II/III Study EXPLORER", *Arthritis and Rheumatism*, vol. 58, no. 12, pp. 4029-4030.

Micheloud, D., Nuno, L., Rodriguez-Mahou, M., Sanchez-Ramon, S., Ortega, M. C., Aguaron, A., Junco, E., Carbone, J., Fernandez-Cruz, E., Carreno, L., & Lopez-Longo, F. J. 2006, "Efficacy and safety of Etanercept, high-dose intravenous gammaglobulin and plasmapheresis combined therapy for lupus diffuse proliferative nephritis complicating pregnancy", *Lupus*, vol. 15, no. 12, pp. 881-885.

Ng, K. P., Cambridge, G., Leandro, M. J., Edwards, J. C., Ehrenstein, M., & Isenberg, D. A. 2007, "B cell depletion therapy in systemic lupus erythematosus: long-term follow-up and predictors of response", *Ann.Rheum.Dis.*, vol. 66, no. 9, pp. 1259-1262.

Petri, M. & Genovese, M. 1992, "Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort", *J Rheumatol.*, vol. 19, no. 10, pp. 1559-1565.

Rovin BH, Teng YKO, Ginzler EM et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2021;397:2070-2080.

Rovin BH, Solomons N, Pendergraft WF 3rd et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int.* 2019;95:219-231

Saxena A, Teng O, Collins C, et al Voclosporin for Lupus Nephritis: Results of the Two-year AURORA 2 Continuation Study *Lupus Science & Medicine* 2022;**9**: doi: 10.1136.

Takahashi, N., Naniwa, T., & Banno, S. 2008, "Successful use of etanercept in the treatment of acute lupus hemophagocytic syndrome", *Mod.Rheumatol.*, vol. 18, no. 1, pp. 72-75.

The EuroQol Group 1990, "EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group", *Health Policy*, vol. 16, no. 3, pp. 199-208.

Trial watch 2009, "Trial watch: BLYS-targeted antibody shows promise in Phase III SLE trial", *Nat.Rev.Drug Discov.*, vol. 8, no. 9, p. 688.

UCB Pharmaceuticals. UCB and Immunomedics announce positive results for epratuzumab phase IIb study in systemic lupus erythematosus (SLE).

www.ucb.com/media-room/newsdetail/?det=1337304 . 2009.

Ref Type: Generic

Appendix 1

Disease in unexposed	Relative risk	unexposed	exposed	Total
5%	2	474	474	948
10%	2	219	219	438
15%	2	133	133	266
20%	2	91	91	182

Using stat calc (epi info) 95% confidence level 80% power 1 to 1 ratio in each cohort